2020 AHA SCORED Study

上海交通大学医学院附属第九人民医院心内科
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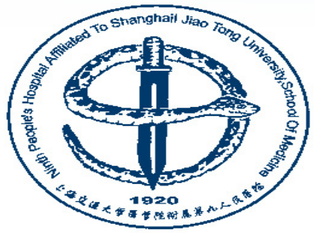

上海交通大學 医学院附属第九人民医院
Shanghai Ninth People's Hospital affiliated to Shanghai JiaoTong University, School of Medicine

研究背景

- SGLT2抑制剂可降低患者因心力衰竭住院的风险。
- 糖尿病患者合并慢性肾脏疾病进一步增加了心力衰竭和缺血性事件的风险。
- 索格列净是一种SGLT2抑制剂，同时也能抑制胃肠道SGLT1。
- 索格列净在糖尿病伴或不伴蛋白尿的慢性肾脏疾病患者中预防心血管事件的有效性和安全性尚未得到很好的研究。

研究方法

- 多中心双盲试验
- 2型糖尿病（糖化血红蛋白水平≥7%）、慢性肾脏疾病（估计肾小球滤过率为25-60 ml/min/1.73m²）和心血管疾病风险的患者按1：1比例随机分配接受索格列净或安慰剂治疗。
- 主要终点被改为因心血管原因而死亡的总人数、因心力衰竭住院人数和因心力衰竭紧急就诊人数的综合结果。

基线结果

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Sotagliflozin (N=5292)	Placebo (N=5292)
Median age (IQR) — yr	69 (63–74)	69 (63–74)
Female sex — no. (%)	2347 (44.3)	2407 (45.5)
Race or ethnic group — no. (%)†		
White	4402 (83.2)	4347 (82.1)
Black	176 (3.3)	188 (3.6)
Asian	317 (6.0)	365 (6.9)
American Indian or Alaska Native	206 (3.9)	216 (4.1)
Native Hawaiian or other Pacific Islander	25 (0.5)	15 (0.3)
Multiple	109 (2.1)	95 (1.8)
Unknown	57 (1.1)	66 (1.2)
Median glycated hemoglobin (IQR) — %	8.3 (7.6–9.3)	8.3 (7.6–9.4)
Median body-mass index (IQR)	31.9 (28.1–36.2)	31.7 (28.0–36.1)
Estimated glomerular filtration rate		
Median (IQR) — ml/min/1.73 m^2	44.4 (37.0–51.3)	44.7 (37.0–51.5)
Distribution — no. (%)		
<30 ml/min/1.73 m^2	419 (7.9)	394 (7.4)
30 to <45 ml/min/1.73 m^2	2347 (44.3)	2308 (43.6)
≥45 ml/min/1.73 m^2	2526 (47.7)	2590 (48.9)
Geographic region — no. (%)		
Eastern Europe	1613 (30.5)	1613 (30.5)
Western Europe	711 (13.4)	709 (13.4)
Latin America	1586 (30.0)	1586 (30.0)
North America	746 (14.1)	747 (14.1)
Rest of the world	636 (12.0)	637 (12.0)
Ejection fraction of ≤40% within past year or hospitalization for heart failure during previous 2 years — no. (%)	1054 (19.9)	1054 (19.9)
History of heart failure — no. (%)‡	1640 (31.0)	1643 (31.0)
Ejection fraction of <40%	505 (9.5)	528 (10.0)
Ejection fraction of 40 to <50%	290 (5.5)	291 (5.5)
Ejection fraction of ≥50%	843 (15.9)	824 (15.6)
Ejection fraction unknown	2 (<0.1)	0
Cardiovascular risk factors — no. (%)		
At least one major	4682 (88.5)	4699 (88.8)
No major, at least two minor	405 (7.7)	413 (7.8)
No major and less than two minor	205 (3.9)	180 (3.4)
Previous myocardial infarction — no. (%)	1051 (19.9)	1057 (20.0)
Previous coronary revascularization — no. (%)	1208 (22.8)	1167 (22.1)
Previous stroke — no. (%)	472 (8.9)	474 (9.0)

Table 1. (Continued.)

Characteristic	Sotagliflozin (N=5292)	Placebo (N=5292)
Urinary albumin-to-creatinine ratio§		
Median (IQR)	74 (18–486)	75 (17–477)
Distribution — no. (%)		
<30	1864 (35.2)	1845 (34.9)
30 to <300	1770 (33.4)	1819 (34.4)
≥300	1658 (31.3)	1628 (30.8)
Median left ventricular ejection fraction (IQR) — %‡	60 (51–64)	60 (51–65)
Median NT-proBNP (IQR) — pg/ml	196.0 (75.1–564.6)	198.1 (74.6–560.7)
Median systolic blood pressure (IQR) — mm Hg	138 (127–149)	139 (127–149)
Median diastolic blood pressure (IQR) — mm Hg	78 (70–85)	78 (70–85)
Any RAAS inhibitor — no. (%)¶	4705 (88.9)	4660 (88.1)
ACE inhibitor	2009 (38.0)	2039 (38.5)
Angiotensin-receptor blocker	2619 (49.5)	2562 (48.4)
Angiotensin receptor–neprilysin inhibitor	66 (1.2)	65 (1.2)
Mineralocorticoid-receptor antagonist	810 (15.3)	776 (14.7)
Beta-blocker — no. (%)	3310 (62.5)	3306 (62.5)
Calcium-channel blocker — no. (%)	2228 (42.1)	2202 (41.6)
Loop diuretic — no. (%)	1869 (35.3)	1867 (35.3)
Other diuretic — no. (%)	1568 (29.6)	1605 (30.3)
Any glucose-lowering medication — no. (%)	5111 (96.6)	5136 (97.1)
Metformin	2907 (54.9)	2955 (55.8)
Sulfonylurea	1400 (26.5)	1486 (28.1)
DPP-4 inhibitor	1041 (19.7)	1044 (19.7)
Insulin	3389 (64.0)	3333 (63.0)
GLP-1 receptor agonist	310 (5.9)	323 (6.1)

研究结果

Table 2. Primary End Point and Secondary End Points.*

End Point	Sotagliflozin (N=5292)	Placebo (N=5292)	Hazard Ratio (95% CI)†	P Value
	no. of events/100 patient-yr (no. of events)			
Primary end point: total no. of deaths from cardiovascular causes, hospitalizations for HF, and urgent visits for HF	5.6 (400)	7.5 (530)	0.74 (0.63–0.88)	<0.001
Major secondary end points, in order of hierarchical testing				
Total no. or hospitalizations for HF and urgent visits for HF	3.5 (245)	5.1 (360)	0.67 (0.55–0.82)	<0.001
Deaths from cardiovascular causes	2.2 (155)	2.4 (170)	0.90 (0.73–1.12)	0.35‡
Total no. of deaths from cardiovascular causes, hospitalizations for HF, nonfatal myocardial infarctions, and nonfatal strokes	7.6 (541)	10.4 (738)	0.72 (0.63–0.83)	—
Total no. of deaths from cardiovascular causes, hospitalizations for HF, urgent visits for HF, and events of HF during hospitalization	6.4 (453)	8.3 (589)	0.76 (0.65–0.89)	—
First occurrence of a sustained decrease of ≥50% in the eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR of <15 ml/min/1.73 m^2 for ≥30 days	0.5 (37)	0.7 (52)	0.71 (0.46–1.08)	—
Deaths from any cause	3.5 (246)	3.5 (246)	0.99 (0.83–1.18)	—
Total no. of deaths from cardiovascular causes, nonfatal myocardial infarctions, and nonfatal strokes	4.8 (343)	6.3 (442)	0.77 (0.65–0.91)	—

* The term eGFR denotes estimated glomerular filtration rate, and HF heart failure.
† Results are presented as point estimates and 95% confidence intervals unadjusted for multiple comparisons, from which no definite conclusions regarding significant differences can be made.
‡ The hierarchical analysis stops after the first P value indicating nonsignificance.

- 索格列净组和安慰剂组的主要终点事件发生率分别为5.6%/病人年和7.5%/病人年（风险比为0.74；95%CI 0.63-0.88；P<0.001）。
- 心血管疾病死亡率，索格列净组为2.2%/病人年，安慰剂组为2.4%/病人年（风险比 0.90；95%CI 0.73-1.12；P=0.35）。
- 对于首次因心血管原因死亡或因心力衰竭住院的复合终点，危险比为0.77（95%CI 0.66-0.91）。

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Table 3. Adverse Events of Special Interest, According to Composite Term.*

Event	Sotagliflozin (N=5291)	Placebo (N=5286)	P Value†
	no. of patients (%)		
Urinary tract infections	610 (11.5)	585 (11.1)	0.45
Diarrhea	448 (8.5)	315 (6.0)	<0.001
Volume depletion	278 (5.3)	213 (4.0)	0.003
Bone fractures	111 (2.1)	117 (2.2)	0.68
Genital mycotic infections	125 (2.4)	45 (0.9)	<0.001
Severe hypoglycemia	53 (1.0)	55 (1.0)	0.84
Malignant conditions	47 (0.9)	42 (0.8)	0.60
Venous thrombotic events	31 (0.6)	37 (0.7)	0.46
Adverse event leading to amputation	32 (0.6)	33 (0.6)	0.89
Diabetic ketoacidosis	30 (0.6)	14 (0.3)	0.02
Pancreatitis	12 (0.2)	20 (0.4)	0.16

与安慰剂组相比，索格列净组发生腹泻、生殖器真菌感染、容量不足和糖尿病酮症酸中毒更常见

结论

- 在糖尿病和慢性肾脏疾病患者中，无论有没有蛋白尿，索格列净组发生心血管原因死亡、因心力衰竭住院和因心力衰竭紧急就诊的综合风险均低于安慰剂组

- 索格列净组不良事件发生率更高。

- 需要进一步更大规模的临床试验研究来评估索格列净对糖尿病和慢性肾脏疾病患者的疗效和安全性

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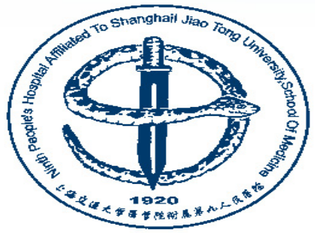

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